Citation:

Canfield MA, Collins JS, Botto LD, Williams LJ, Mai CT, Kirby RS, Pearson K, Devine O, Mulinare J. Changes in the birth prevalence of selected birth defects after grain fortification with folic acid in the United States: Findings from a multi-state population-based study. *Birth Defects Res A Clin Mol Teratol* 2005; 73: 679-689.

PubMed ID: 16240378

Study Design:

Trend study

Class:

D - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

The purpose of this study was to examine whether folic acid fortification may have decreased the prevalence of birth defects other than neural tube defects.

Inclusion Criteria:

- Population-based registries containing data on the following birth defects: Anecephaly, spina bifida without anencephaly, common truncus, transposition of the great arteries, tetralogy of Fallot, ventricular septal defects, cleft palate only, cleft lip with or without cleft palate, pyloric stenosis, renal agenesis, bladder exstrophy, obstructive genitourinary defects, reduction defects of the upper and lower limbs, omphalocele and down syndrome.
- Population-based registries containing complete data for entire study period (1995-2000)
- Data from two delivery periods (1995-1996 and 1999-2000).

Exclusion Criteria:

- Programs with incomplete data for all or portions of the study period
- Programs with unspecific data or limitations in their coding systems for specific birth defects d ata from 1997 to 1998 (this data includes pregnancies that occurred during the period of implementation of fortification and was omitted to sharpen the analytical contrast between pre- and post-fortification time periods).

Description of Study Protocol:

Recruitment

- Birth rate data were obtained from population-based registries from the following states: Arkansas, California, Colorado, Delaware, Georgia, Hawaii, Illinois, Iowa, Kentucky, Maryland, Michigan, Missouri, North Carolina, New Jersey, New Mexico, New York, Oklahoma, Puerto Rico, Rhode Island, South Carolina, Utah, Virginia and West Virginia
- Eight of the 23 programs included data on birth defects among pregnancy terminations (prenatally diagnosed cases).

Design

- Data on the prevalence of 16 birth defects were collected from state registries during the time periods of 1995 to 1996 and 1999 to 2000
- Changes in birth prevalence between the two time periods were assessed by calculating prevalence ratios and 95% confidence intervals for each defect.

Statistical Analysis

- The prevalence ratio was determined for each defect (prevalence in 1999 to 2000 divided by the prevalence in 1995 to 1996)
- The Taylor series method was used to calculate 95% confidence intervals for each prevalence ratio
- Results were stratified by race or ethnicity and by programs with or without prenatal ascertainment
- The study had 70 to 80% power to detect a 10% difference in prevalence for all but three defects (common truncus, omphalocele and lower limb reduction defects)
- Small number of cases were found for several defects (including common truncus, omphalocele and bladder exstrophy).

Data Collection Summary:

- *Timing of measurements:* Data on the prevalence of birth defects was collected during the years 1995 to 1996 and again from 1999 to 2000
- *Dependent variables:* Prevalence ratio of birth defects (prevalence in 1999 to 2000 divided by the prevalence in 1995 to 1996)
- *Independent variables:* Folic acid fortification of grains in the United States
- *Control variables:*
    - Race and ethnicity
    - Prenatal ascertainment of cases.

Description of Actual Data Sample:

- *Initial N:* N/A
- *Attrition (final N):* N/A
- *Age:* Prenatal terminations and live births
- *Ethnicity:* Hispanic, non-Hispanic Whites, non-Hispanic Blacks

  Other relevant demographics: not listed

- *Anthropometrics:* Not listed

- *Location:* Multi-state data from the United States.

Summary of Results:

Table 1: **Prevalence Ratios of Defects 1995 to 2000**

Defect	Prevalence Ratio	95% CI	P-Value	Estimated Percentage Change
Anencephaly	0.84	0.76-0.94	P<	-16
Spina Bifida	0.66	0.61-0.71	P<	-34
Common Truncus	0.88	0.72-1.08	P ≥	-12
Transposition of great arteries	0.88	0.81-0.96	P<	-12
Tetralogy of Fallot	0.96	0.88-1.04	P ≥	-4
Ventricular septal defect	0.97	0.94-1.00	P ≥	-3
Cleft palate only	0.88	0.82-0.95	P<	-12
Cleft lip or palate	0.95	0.90-1.00	P ≥	-5
Pyloric stenosis	0.95	0.90-0.99	P<	-5
Renal agenesis	0.92	0.84-1.01	P ≥	-8
Bladder exstrophy	1.13	0.82-1.55	P ≥	13
Obstructive genitourinary defects	1.12	1.07-1.16	P<	12
Upper limb reduction defects	0.89	0.80-0.99	P<	-11
Lower limb reduction defects	0.97	0.84-1.11	P ≥	-3
Omphalocele	0.79	0.66-0.95	P<	-21
Down Syndrome	1.06	1.01-1.11	P<	6

Racial and ethnic patterns were not consistent.

- Among congenital heart defects, the only ethnic-specific significant decrease in prevalence was for common truncus among Hispanics (prevalence ratio 0.55, 95% CI 0.31-0.98, P<0.05)
- Cleft palate declined significantly only among non-whites (20% and 22% reductions for Hispanic and black births, respectively)
- Down syndrome prevalence rose overall, but the only significant race-specific increase occurred among black births (16%).

Prevalence ratios appeared to vary for some defects depending on the programs' availability of prenatal ascertainment.

- The five non-NTD's showing significant overall declines in prevalence (transposition of the great arteries, cleft palate, pyloric stenosis, upper limb reduction defects, and omphalocele) showed significant reductions only among states without prenatal data
- For cleft lip with or without cleft palate and renal agenesis, significant reductions in

prevalence (13% and 28%, respectively) were seen only in states with prenatal surveillance
- The significant declines for spina bifida and anencephaly were observed in both groups of registries
- The increases in obstructive genitourinary defects and down syndrome were seen only in registries without prenatal surveillance.

Author Conclusion:

- The results from this study suggest some modest benefit from the folic acid fortification on the prevalence of birth defects other than NTD's (neural tube defects). Previously reported reductions in the birth prevalence of NTD's were confirmed.
- Modest but statistically significant reductions were found in the birth prevalence for transposition of the great arteries, cleft palate only, pyloric stenosis, upper limb reduction defects and omphalocele
- More substantial sub-group differences were found for renal agenesis among programs that conduct prenatal surveillance, for common truncus among Hispanics and for upper limb reduction defects among Hispanics.

Reviewer Comments:

- *Details regarding the data from the state registries were not available in this paper*
- *Possible confounding factors such as maternal age, health condition or diet were not controlled for in this analysis.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions		
1.	**Was the research question clearly stated?**	Yes

1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	No
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	**Were study groups comparable?**	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	???
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	???
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A

4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	???
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	No
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	No
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	???
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A

7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	N/A
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes